AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1. (Previously Presented) A method for evaluating specificity of a drug comprising comparing activity of a drug against its target pathway (D_{target}) in a biological sample and activity of said drug against at least one of its off-target pathways ($D_{\text{off-target}}$) in said biological sample, wherein said D_{target} and $D_{\text{off-target}}$ are represented by quantities selected from the group consisting of (i)

$$D_{\text{target}} = R_{\text{target},k}(\alpha_{\text{target}}, t_l) \text{ and}$$

$$D_{\text{off-target}} = R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l), \text{ respectively;}$$

(ii)

$$D_{\text{target}} = \sum_k \beta_k R_{\text{target},k}(\alpha_{\text{target}}, t_l) \text{ and}$$

$$D_{\text{off-target}} = \sum_k \beta_k R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l), \text{ respectively; and (iii)}$$

$$D_{\text{target}} = C_{\text{target}} \text{ and } D_{\text{off-target}} = C_{\text{off-target}}, \text{ respectively;}$$

wherein α_{target} is a scaling constant of a scaling transformation of said target pathway, $\alpha_{\text{off-target}}$ is a scaling constant of a scaling transformation of said at least one of its off-target pathways, $R_{\text{target},k}(\alpha_{\text{target}}, t_l)$ is a scaled response of cellular constituent k in said target pathway and $R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l)$ is a scaled response of cellular constituent k in said at least one of its off-target pathways, t_l is a drug exposure level, β_k is a constant for cellular constituent k, C_{target} is the minimal level of said drug to achieve a threshold response in said target pathway, and $C_{\text{off-target}}$ is the minimal level of said drug to achieve a

threshold response in said at least one of its off-target pathways; thereby evaluating specificity of said drug.

2. (Previously Presented) The method of Claim 1 wherein said D_{target} and $D_{\text{off-target}}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents in said biological sample at each level of said drug to obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional in said test sample, and measuring said plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

c) determining said D_{target} and $D_{\text{off-target}}$ by comparing said first and second profiles.

3. (Previously Presented) The method of claim 2 wherein said biological sample is a yeast cell, and said test sample is a yeast cell in which a critical gene in said target pathway is deleted.

4. (Previously Presented) The method of claim 2 wherein said biological sample is a mammalian cell, and said test sample is a mammalian cell in which a critical gene in said target pathway is deleted.

5. (Previously Presented) The method of claim 2 wherein said biological sample is an animal, and said test sample is a transgenic animal in which a critical gene in said target pathway is made nonfunctional.

6. (Previously Presented) The method of claim 2 wherein said plurality of cellular constituents is a plurality of transcripts of a plurality of genes.

7. (Previously Presented) The method of claim 2 wherein said plurality of cellular constituents is a plurality of proteins.

8. (Previously Presented) The method of claim 1 wherein said D_{target} and $D_{\text{off-target}}$ are measured according to a method comprising:

a) perturbing said target pathway and/or said off target pathway in said biological sample to obtain a perturbation profile consisting of measurements of a plurality of cellular constituents;

b) applying a plurality of levels of said drug to said biological sample to obtain a drug response profile consisting of measurements of said plurality of cellular constituents at each level of said drug; and

c) determining said D_{target} and $D_{\text{off}-\text{target}}$ by comparing said drug response profile and said perturbation profile.

9. (Previously Presented) The method of claim 8 wherein said plurality of cellular constituents is a plurality of transcripts of a plurality of genes.

10. (Previously Presented) The method of claim 8 wherein said plurality of cellular constituents is a plurality of proteins.

11. (Currently Amended) A method for evaluating specificity of a drug comprising comparing activity of a drug against its target pathway (D_{target}) in a ~~biological sample~~ cell and activity of said drug against at least one of its off-target pathways ($D_{\text{off}-\text{target}}$) in said ~~biological sample~~ cell, wherein said D_{target} and $D_{\text{off}-\text{target}}$ are each determined based on measurements of a plurality of cellular constituents of said cell, and wherein said comparing step comprises calculating a specificity index (SI) according to the following formula:

$$\text{SI} = \frac{n \bullet D_{\text{target}}}{\sum D_{\text{off}-\text{target}}}$$

wherein: n is the number of off-target pathways.

12. (Previously Presented) A method for evaluating specificity of a drug comprising:

a) measuring activity of a drug against its target pathway to obtain a target activity (D_{target});

b) measuring activity of said drug against at least one pathway other than said target pathway to obtain at least one off-target activity ($D_{\text{off}-\text{target}}$); and

c) determining said specificity by comparing said D_{target} and said $D_{\text{off}-\text{target}}$;

wherein said D_{target} and $D_{\text{off}-\text{target}}$ are represented by quantities selected from the group consisting of (i)

$$D_{\text{target}} = R_{\text{target},k}(\alpha_{\text{target}}, t_l) \text{ and}$$

$$D_{\text{off}-\text{target}} = R_{\text{off}-\text{target},k}(\alpha_{\text{off}-\text{target}}, t_l), \text{ respectively;}$$

(ii)

$$D_{\text{target}} = \sum_k \beta_k R_{\text{target},k}(\alpha_{\text{target}}, t_l) \text{ and}$$

$$D_{\text{off}-\text{target}} = \sum_k \beta_k R_{\text{off}-\text{target},k}(\alpha_{\text{off}-\text{target}}, t_l), \text{ respectively; and (iii)}$$

$$D_{\text{target}} = C_{\text{target}} \text{ and } D_{\text{off}-\text{target}} = C_{\text{off}-\text{target}}, \text{ respectively;}$$

wherein α_{target} is a scaling constant of a scaling transformation of said target pathway, $\alpha_{\text{off-target}}$ is a scaling constant of a scaling transformation of said at least one of its off-target pathways, $R_{\text{target},k}(\alpha_{\text{target}}, t_l)$ is a scaled response of cellular constituent k in said target pathway and $R_{\text{off}-\text{target},k}(\alpha_{\text{off}-\text{target}}, t_l)$ is a scaled response of cellular constituent k in said at least one of its off-target pathways, t_l is a drug exposure level, β_k is a constant for cellular constituent k, C_{target} is the minimal level of said drug to achieve a threshold response in said target pathway and $C_{\text{off-target}}$ is the minimal level of said drug to achieve a threshold response in said at least one of its off-target pathways.

13. (Previously Presented) The method of claim 12 wherein said D_{target} and $D_{\text{off}-\text{target}}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents in said biological sample at each level of said drug to obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional

in said test sample, and measuring said plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

c) determining said D_{target} and $D_{\text{off}-\text{target}}$ by comparing said first and second profiles.

14. (Previously Presented) The method of claim 13 wherein said plurality of cellular constituents is a plurality of transcripts of a plurality of genes.

15. (Previously Presented) The method of claim 13 wherein said plurality of cellular constituents is a plurality of proteins.

16. (Previously Presented) The method of claim 13 wherein said biological sample is a yeast cell, and said test sample is a yeast cell in which a critical gene in said target pathway is deleted.

17. (Previously Presented) The method of claim 13 wherein said biological sample is a mammalian cell, and said test sample is a mammalian cell in which a critical gene in said target pathway is deleted.

18. (Previously Presented) The method of claim 13 wherein said biological sample is an animal, and said test sample is a transgenic animal in which a critical gene in said target pathway is made nonfunctional.

19. (Previously Presented) The method of claim 12 wherein said D_{target} and $D_{\text{off}-\text{target}}$ are measured according to a method comprising:

a) perturbing said target pathway and/or said off target pathway in said biological sample to obtain a perturbation profile consisting of measurements of a plurality of cellular constituents;

b) applying a plurality of levels of said drug to said biological sample to obtain a drug response profile consisting of measurements of said plurality of cellular constituents at each level of said drug; and

c) determining said D_{target} and $D_{\text{off}-\text{target}}$ by comparing said drug response profile and said perturbation profile.

20. (Previously Presented) The method of claim 19 wherein said plurality of cellular constituents is a plurality of transcripts of a plurality of genes.

21. (Previously Presented) The method of claim 20 wherein said plurality of cellular constituents is a plurality of proteins.

22. (Currently Amended) A method for evaluating specificity of a drug comprising:

a) ~~measuring~~ determining activity of a drug against its target pathway in a cell to obtain a target activity (D_{target});

b) ~~measuring~~ determining activity of said drug against at least one pathway other than said target pathway in said cell to obtain at least one off-target activity ($D_{\text{off}-\text{target}}$); and

c) determining said specificity by comparing said D_{target} and said $D_{\text{off}-\text{target}}$;

wherein said D_{target} and $D_{\text{off}-\text{target}}$ are each determined based on measurements of a plurality of cellular constituents of said cell, and wherein said determining step comprises calculating a specificity index (SI) according to the following formula:

$$\text{SI} = \frac{n \bullet D_{\text{target}}}{\sum D_{\text{off}-\text{target}}}$$

wherein: n is the number of off-target pathways.

Claims 23-63 (Canceled).

64. (Previously Presented) A method for evaluating specificity of a drug, said method comprising:

(a) decomposing a drug response profile into one or a combination of pathway response profiles, wherein said drug response profile comprises measurements of a plurality of cellular constituents in a biological sample in response to said drug over a plurality of levels of drug exposure, and each said pathway response profile comprises measurements of said plurality of cellular constituents at a plurality of levels of perturbation to a biological pathway, said decomposing comprising representing said drug response profile in terms of said one or a combination of pathway response profiles according to equation

$$D_k(t_l) \cong \sum_i R_{i,k}(\alpha_i, t_l)$$

wherein t_l is a level of the drug, α_i is a scaling constant of a scaling transformation of pathway i, $D_k(t_l)$ is the measurement of cellular constituent k in said drug response profile at the drug exposure level of t_l, $R_{i,k}(\alpha_i, t_l)$ is the measurement of cellular constituent k in pathway i at the drug exposure level of t_l; and

(b) comparing, among said one or a combination of pathway response profiles, the pathway response profiles for the one or more biological pathways associated with therapeutic effects of the drug with the pathway response profiles for the one or more biological pathways that are associated with one or more non-therapeutic effects of the drug, thereby evaluating specificity of said drug.

65. (Previously Presented) A method for evaluating specificity of a drug, said method comprising:

(a) decomposing a drug response profile into one or a combination of pathway response profiles, wherein said drug response profile comprises measurements of a plurality of cellular constituents in a biological sample in response to said drug over a plurality of levels of drug exposure, and each said pathway response profile comprises measurements of said plurality of cellular constituents at a plurality of levels of perturbation to a biological pathway, and wherein said decomposing comprises transforming said levels of drug exposure into said levels of perturbation by a horizontal scaling transformation; and

(b) comparing, among said one or a combination of pathway response profiles, the pathway response profiles for the one or more biological pathways associated with therapeutic effects of the drug with the pathway response profiles for the one or more biological pathways that are associated with one or more non-therapeutic effects of the drug, thereby evaluating specificity of said drug.

66. (Previously Presented) The method of claim 65, wherein said horizontal scaling transformation is a linear transformation.

67. (Previously Presented) The method of claim 65, wherein said decomposing comprises determining said scaling transformation such that said drug response profile is represented by said one or a combination of pathway response profiles.

68. (Previously Presented) The method of claim 67, wherein said determining is by a method comprising least squares minimizing the residue between said drug response profile and said one or a combination of pathway response profiles.

69. (Previously Presented) The method of claim 65, wherein values of said measurements of a plurality of cellular constituents have been converted into cellular constituent set values.

70. (Previously Presented) A method for evaluating specificity of a drug, said method comprising decomposing a drug response profile into one or a combination of pathway response profiles, wherein said drug response profile comprises measurements of a plurality of cellular constituents in a biological sample in response to said drug over a plurality of levels of drug dosage, and each said pathway response profile comprises measurements of said plurality of cellular constituents at a plurality of levels of perturbation to a biological pathway, said decomposing comprising representing said drug response profile in terms of said one or a combination of pathway response profiles according to equation

$$D_k(t_l) \cong \sum_i R_{i,k}(\alpha_i, t_l)$$

wherein t_l is a level of the drug, α_i is a scaling constant of a scaling transformation of pathway i, $D_k(t_l)$ is the measurement of cellular constituent k in said drug response profile at the drug exposure level of t_l, $R_{i,k}(\alpha_i, t_l)$ is the measurement of cellular constituent k in pathway i at the drug exposure level of t_l; and comparing among said one or a combination of pathway response profiles, the pathway response profiles for the one or more biological pathways associated with therapeutic effects of the drug with the pathway response profiles for the one or more biological pathways that are associated with one or more non-therapeutic effects of the drug, thereby evaluating specificity of said drug.

71. (Previously Presented) The method of claim 67 or 68, wherein said comparing comprises comparing activity of said drug on its target pathway (D_{target}) and at least one of its off-target pathways ($D_{\text{off-target}}$), wherein said D_{target} and said $D_{\text{off-target}}$ are calculated according to equations

$$D_{\text{target}}(t_l) = \sum_k \beta_k R_{\text{target},k}(\alpha_{\text{target}}, t_l)$$

and

$$D_{\text{off-target}}(t_l) = \sum_k \beta_k R_{\text{off-target,k}}(\alpha_{\text{off-target}}, t_l)$$

where t_l is a level of the drug, β_k is a constant for cellular constituent k, α_{target} is a scaling constant of said scaling transformation of said target pathway, $\alpha_{\text{off-target}}$ is a scaling constant of said scaling transformation of said off-target pathway, and $R_{\text{target},k}(\alpha_{\text{target}}, t_l)$ is the response of cellular constituent k in the target pathway at the drug level t_l and $R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l)$ is the response of cellular constituent k in the off-target pathway at the drug level t_l.

72. (Previously Presented) The method of claim 71, wherein said comparing said D_{target} and said $D_{\text{off-target}}$ comprises calculating a specificity index (SI) according to the following formula:

$$\text{SI} = \frac{n \bullet D_{\text{target}}}{\sum D_{\text{off-target}}}$$

wherein: n is the number of off-target pathways.

73. (Previously Presented) The method of claim 64 or 70, wherein said comparing is carried out by a method comprising comparing $R_{\text{target},k}(\alpha_{\text{target}}, t_l)$ with $R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l)$; or $\sum_k \beta_k R_{\text{target},k}(\alpha_{\text{target}}, t_l)$ with $\sum_k \beta_k R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l)$; wherein $R_{\text{target},k}(\alpha_{\text{target}}, t_l)$ is a scaled response of cellular constituent k in a pathway associated with therapeutic effects of the drug, $R_{\text{off-target},k}(\alpha_{\text{off-target}}, t_l)$ is a scaled response of cellular constituent k in a pathway

associated with one or more non-therapeutic effects of the drug, and β_k is a constant for cellular constituent k.

74. (Previously Presented) The method of claim 1 or 12, wherein said comparing said D_{target} and said $D_{\text{off}-\text{target}}$ comprises calculating a specificity index (SI) according to the following formula:

$$\text{SI} = \frac{n \bullet D_{\text{target}}}{\Sigma D_{\text{off}-\text{target}}}$$

wherein: n is the number of off-target pathways.

75. (New) The method of claim 11 or 22, wherein said measurements of a plurality of cellular constituents are measurements of levels of gene transcripts.

76. (New) The method of claim 11 or 22, wherein said measurements of a plurality of cellular constituents are measurements of levels of proteins.